Editorial: "Disease-Only" Alleles and Genotypes in Complex Disorders?

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IRJ covers a wide range of topics in the fields of social welfare and rehabilitation sciences. Schizophrenia (SCZ) is one of the relevant topics, which associates with enormous psychological and economic burden on the affected families. This multifactorial and debilitating disorder is largely influenced by genetic factors. Although several genes and risk factors have been reported for SCZ, the role of those genes is speculated to be minor in the pathogenesis or the course of the illness. Imbalanced higher brain functions such as cognition are the predominant component of SCZ. Since the higher order brain functions are essentially human-specific, it may be hypothesized that human-specific genetic factors are of prime importance in the causation of SCZ [1].

An endeavor to identify human-specific genetic factors and their role in SCZ patients has resulted in the discovery of alleles and genotypes at the extreme end of Short Tandem Repeats (STRs) that occur with disease only. Those alleles and genotypes appear to be non-existent in the control pool (so-called "disease-only"). The Ras like without CAAX 2 gene (RIT2) is regulated by one of the longest STRs identified in a human gene core promoter, expansion of which may be of selective advantage in human-specific characteristics. In line with the above notion, the predominant allele of the RIT2 core promoter STR is human-specific in length [2].

Indeed, this STR is the first instance of selective advantage for a human-specific allele at an STR locus. The shortest allele, at 5-repeats, was detected in the homozygous status in consanguineous SCZ. Of evolutionary implication, the 5-repeat allele is reported in indigenous hunter-gatherer men from southern Africa [3]. It is reasonable to hypothesize that alleles that are linked to adaptive and human-specific evolutionary characteristics (e.g. cognition) are also linked to major psychiatric disorders.

In contrast with the previous hypotheses that genetic factors only modify disease risk, there may be "disease-only" alleles and genotypes in complex disorders that are lacking in the control pool. "Disease-only" alleles and genotypes may change our perspective of complex disorders, and provide genetic models similar to single-gene disorders. Future studies of similar genetic factors in complex disorders may shed more light on this vastly enigmatic aspect of disease pathogenesis in complex disorders.

*** Corresponding Author:**
Mina Ohadi, PhD
Address: *Iranian Research Center on Aging, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.*
E-mail: *ohadi.mina@yahoo.com*

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